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(54) Title: PEPTIDES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

(57) Abstract

The present invention relates generally to peptide sequences, and methods of their use, which sequences modulate the activity of anti-idiotypic T cells. The activity of the anti-idiotypic T cells of interest is related to the ability of these T cells to recognize anti-p277 T cells. The peptides of the present invention thus comprise important tools in the effort to diagnose, prevent, alleviate or treat disease related to insulin-dependent diabetes mellitus (IDDM).

PEPTIDES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

Field of the Invention

5   The present invention relates generally to peptide
sequences, and methods of their use, which sequences modulate
the activity of anti-idiotypic T cells. The activity of the
anti-idiotypic T cells of interest is related to the ability
of these T cells to recognize anti-p277 T cells. The peptides
10   of the present invention thus comprise important tools in the
effort to diagnose, prevent, alleviate or treat disease
related to insulin-dependent diabetes mellitus (IDDM).

Background of the Invention

15   Type I diabetes, or IDDM, is an autoimmune disease
caused by T cells that attack and destroy the insulin-
producing cells located in the islets of the pancreas (23).
The autoimmune process culminating in IDDM begins and
progresses without symptoms. The disease surfaces clinically
20   only when the cumulative loss of β-cells exceeds the
capacity of the residual β-cells to supply insulin. Indeed,
the collapse of glucose homeostasis and clinical IDDM is
thought to occur only after 80-90% of the β-cells have been
inactivated by the immune system. Thus, patients who can be
25   identified as suffering from IDDM are bound to be in an
advanced stage of autoimmune destruction of their β-cells.
Moreover, diagnosis of incipient, pre-clinical diabetes by the
detection of immunological markers of β-cell autoimmunity
can be made only after the onset of the autoimmune process.
30   Therefore, the therapeutic quest is to find a safe, specific
and effective way to turn off an autoimmune process that is
already well underway.
         The present inventors have examined this question
before by studying the spontaneous diabetes developing in mice
35   of the NOD strain, which is considered to be a faithful model
of human IDDM (23-25). NOD mice develop insulitis around one
month of age, which begins as a mild peri-isl t infiltrate and
progresses to severe intra-islet inflammation. Hyperglycemia,

which attests to insulin insufficiency, begins in the females
in our colony at about three months of age. By six months of
age, almost all the female NOD mic have developed severe
diabetes and most die in the absence of insulin treatment.

5   Male NOD mice have a lower incidence of disease, for reasons
that are not clear. The diabetes of NOD mice has been shown
to be caused by autoimmune T cells (26).

       T cell reactivity and auto-antibodies to various
antigens have been detected in human IDDM patients as well as

10   in NOD mice (27), and it is not clear whether immunity to any
single one of the possible target antigens is the primary
cause of the disease. Beyond the question of causation is the
question of therapy.

       It has been demonstrated that the initiation of the

15   autoimmune process in NOD mice can be prevented by subjecting
the mice, before the onset of diabetes, to various
manipulations such as restricted diet, viral infections, or
non-specific stimulation of the immune system (24). NOD
diabetes is also preventable by induction of immunological

20   tolerance in pre-diabetic mice to the antigen glutamic acid
decarboxylase (GAD) (28, 29).

       Anti-idiotypic T cells are T cells that recognize
peptides derived from the antigen receptors of other T cells
(6). It is thought that anti-idiotypic T cells are involved

25   in regulating the activities of the T cells whose T cell
receptor (TCR) peptides they recognize. Autoimmune T cells
might be subject to regulation by anti-idiotypic T cells:
anti-idiotypic T cells have been detected following
intentional T cell vaccination of rodents in the model of

30   experimental autoimmune encephalomyelitis (EAE) (6) or of
humans (7) suffering from multiple sclerosis (MS) with
autoimmune T cells.

       European patent application 261,648 discloses the
use of activated T cells specific for an autoimmune disease

35   for the treatment of such disease. The T cells are preferably
first pressure treated, subjected to a chemical cross-linking
agent and/or subjected to a cytoskeletal disrupting agent in
order to improve their immunogenicity. The entire treated

CLAIMS

1. A peptide having at least 7 and preferably about
7-24 amino acid residues, substantially corresponding to a
"VDJ" region of the formula

                            V-D-J
in which "V" includes the dipeptide sequence A-S, "D",
preferably having 2-5 amino acid residues, includes the
dipeptide sequence L-G, and "J" includes the tripeptide
sequence N-Q-D, or a salt or functional derivative thereof.

2. The peptide of claim 1 in which "V" includes the
tripeptide sequence A-S-S.

3. The peptide of claim 1 in which "D" includes the
tripeptide sequence L-G-G, the tripeptide sequence R-L-G or
the pentapeptide sequence L-G-L-G-A (residues 4-8 of SEQ ID
NO:4).

4. The peptide of any of claims 1-3, wherein the
dipeptide sequence A-S of "V" is part of the tripeptide
adjacent to "D".

5. The peptide of any of claims 1-5, wherein the
tripeptide sequence N-Q-D of "J" is adjacent to "D".

6. The peptide of any of claims 1-5, wherein "V"
comprises a "Vβ" segment which segment includes at least a
portion of the C-terminal end of a protein encoded by a Vβ
gene.

7. The peptide of claim 6, wherein the C-terminal
tripeptide sequence of said Vβ segment includes the
dipeptide sequence A-S.

8. The peptide of claim 6 in which said segment
includes from 1 to about 10 amino acid residues of the C-
terminal end of the protein encoded by the Vβ gene.

9. The peptide of claim 6, in which said Vβ gene
is selected from the group consisting of Vβ6, Vβ8, Vβ12,
and Vβ16.

10. The peptide of any claims 1-3, wherein "J"
comprises a "Jβ" segment which segment includes at least a
portion of the N-terminal end of a portion encoded by a Jβ
gene.

11. The peptide of claim 10, wherein the N-terminal
tripeptide sequence of said Jβ segment is N-Q-D.

12. The peptide of claim 10 in which said segment
includes from 1 to about 10 amino acid residues of the N-
terminal end of the protein encoded by the Jβ gene.

13. The peptide of claim 10 in which said Jβ gene
is Jβ2.5.

14. A peptide having up to about 24 amino acid
residues comprising the sequence A-S-S-L-G-G-N-Q-D (residues
47-55 of SEQ ID NO:1).

15. A peptide having up to about 24 amino acid
residues comprising the sequence A-S-R-L-G-N-Q-D (SEQ ID
NO:3).

16. A peptide having up to about 24 amino acid
residues comprising the sequence A-S-S-L-G-L-G-A-N-Q-D (SEQ ID
NO:4).

17. A peptide having up to about 24 amino acid
residues comprising the sequence A-S-S-L-G-A-N-Q-D (SEQ ID
NO:16).

18.   A DNA construct comprising a polynucleotide sequence encoding the peptide of any of claims 1-3 or 14-17, or its complement.

19.   A pharmaceutical composition comprising a peptide of any of claims 1-3 or 14-17.

20.   The pharmaceutical composition of claim 19 which is a vaccine.

21.   An agent for detecting the presence of anti-idiotypic T cells involved in the recognition of anti-p277 T cells comprising a peptide of any of claims 1-3 or 14-17.

22.   The agent of claim 21 which is conjugated to a detectable label.

23.   A conjugate comprising the peptide of any of claims 1-3 or 14-17 and a second molecule.

24.   The conjugate of claim 23 in which said second molecule is a polypeptide.

25.   The conjugate of claim 23 in which said second molecule is a small organic molecule.

26.   A method of modulating anti-idiotypic T cell activity in an individual, said activity associated with the ability of anti-idiotypic T cells to recognize anti-p277 T cells, comprising administering to the individual an amount of a peptide in accordance with any of claims 1-3 or 14-17 effective to regulate the activity of said anti-idiotypic T cells.

27.   The method of claim 26 in which said activity is potentiated.